REMARKS

I. Status Summary

Claims 8, 20, and 26-29 are pending in the present application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office") in a Final Official Action dated October 8, 2008 (hereinafter the "Final Official Action"). A Notice of Appeal and After Final Amendment G were filed on May 9, 2009, but After Final Amendment G was not entered. Applicants respectfully request that After Final Amendment G not be entered, and that the instant After Final Amendment H be entered and the instant prosecution continue based on After Final Amendment H.

Claims 26 and 29 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement.

Claims 26 and 29 have also been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite.

Claims 8, 20, and 26-29 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by U.S. Patent No. 5,683,894 to Edwards *et al.* (hereinafter referred to as "Edwards").

Claims 8, 20, and 26-29 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over U.S. Patent No. 5,169,762 to Gray & Ullrich (hereinafter "Gray & Ullrich") and U.S. Patent No. 5,235,043 to Collins *et al.* (hereinafter "Collins").

Claims 26 and 29 have been amended. Support for the amendments can be found throughout the specification as filed, including at page 22, line 28, through page 29, line 3. Thus, no new matter has been added by the amendments to claims 26 and 29.

Reconsideration of the application as amended and based on the remarks set forth below is respectfully requested.

II. Response to the Rejection under 35 U.S.C. § 112, First Paragraph

The Patent Office has rejected claims 26 and 29 under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement upon the contention that the phrase "less than about twice that of rh β-NGF on a molar basis" constitutes new matter.

Applicants respectfully disagree with the Patent Office's assertions with respect to the instant rejection. However, without acquiescing to the Patent Office's contentions, applicants have amended claims 26 and 29 to remove the phrase at issue and replace the same with the

phrase "wherein the human proNGF has a biological activity in a dorsal root ganglion (DRG) assay that is about half that of human β-NGF in the same assay on a molar basis". Support for the amendment to claims 26 and 29 can be found in the specification as filed, including particularly at page 22, line 28. through page 29, line 3. Thus, no new matter has been added by the amendments to the claims.

Applicants respectfully submit that as a result of the amendments, the instant new matter rejection of claims 26 and 29 under 35 U.S.C. § 1112, first paragraph, have been rendered moot. As such, applicants respectfully request that the instant rejection be withdrawn at this time.

III. Response to the Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 26 and 29 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "less than about twice" renders the claims indefinite.

Applicants respectfully disagree. Nonetheless, and without acquiescing to the Patent Office's assertions, applicants have amended claims 26 and 29 to delete the phrase at issue. As such, applicants respectfully submit that the instant rejection has been rendered moot, and respectfully request that it be withdrawn at this time.

IV. Response to the Rejection under § 102

Claims 8, 20, and 26-29 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by U.S. Patent No. 5,683,894 to Edwards *et al.* (hereinafter referred to as "Edwards"). According to the Patent Office, Edwards "teaches how to make a pharmaceutical composition comprising a recombinant pro-NGF-beta solution 'derived from humans' (e.g., col. 4, lines 40-42)" (*see* Final Official Action at page 5).

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that col. 4, lines 40-42 of Edwards recites the following: "In general, a gene encoding pro-NGF-beta is first isolated from the desired species (e.g., human, murine, bovine, etc.) using methods known in the art". Applicants respectfully submit that there is no disclosure in this passage of a "pharmaceutical preparation comprising purified human proNGF as the active ingredient, wherein the purified human proNGF is purified to at least 90% purity and has an activity in vivo analogous to β-NGF and promotes survival of dorsal root ganglia (DRG) sensory neurons" as recited in claim 8 or a "pharmaceutical preparation according to claim 8, wherein the human proNGF has a biological activity in a dorsal

root ganglion (DRG) assay that is about half that of human β-NGF in the same assay on a molar basis" as recited in claim 26. At best, applicants respectfully submit that this passage provide a mere invitation to experiment to identify a human pro-NGF-beta. There is no teaching of making a pharmaceutical preparation, and thus Edwards does not support a rejection of the instant claims under 35 U.S.C. § 102(b).

Additionally, applicants respectfully submit that the Patent Office's reliance on *In re Heck*, *Merck*, and *Upsher-Smith Labs* is misplaced. For example, the Patent Office relies on *In re Heck* for the proposition that references are "relevant for all they contain". Applicants respectfully submit, however, that since Edwards does not contain a disclosure of a pharmaceutical preparation containing a human proNGF, it cannot be read to "contain" such disclosure.

Furthermore, the Patent Office's assertion that a reference "may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art" from *Merck* also fails to support a rejection under 35 U.S.C. § 102. It is noted that *Merck* is a case that examines patentability under 35 U.S.C. § 103: its holding is not applicable to examination under 35 U.S.C. § 102.

Additionally, the Patent Office's reliance on *Upsher-Smtih Labs* and related cases is also misplaced. In each of these cases, the reference explicitly disclosed the subject matter of the rejected claims. Thus, these cases involve a set of facts that is not present in the instant case, and thus fails to support the instant rejection.

Continuing, it is noted that this issue in discussed in M.P.E.P. § 2131.05, which states in part:

> A reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims (emphasis added).

M.P.E.P. § 2131.05 continues:

> A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis. Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (emphasis added).

Thus, in each case, the key circumstance that is missing from the instant set of facts and that is thus fatal to the Patent Office's assertions with respect to the current anticipation rejection is that Edwards does not disclose the subject matter of the instant claims.

And finally, applicants respectfully submit that the Patent Office has presented no evidence or other reasoned argument that supports the contention that Edwards discloses a pharmaceutical composition. Example 2 of Edwards does not support the instant rejection as Example 2 teaches the *in vitro* expression of mouse pro-NGF-beta, and the translation of the same using a wheat germ extract in the presence of ^{35}S-methionine. It is submitted that one of ordinary skill in the art would recognize that a pharmaceutical composition would never contain ^{35}S-methionine, and the Patent Office may not disregard this fact when it attempts to apply this reference to the instant claims.

Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of anticipation of claims 8, 20, and 26-29 over Edwards. Accordingly, applicants respectfully request that the instant rejection be withdrawn at this time.

V. Response to the Rejection under § 103

Claims 8, 20, and 26-29 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over U.S. Patent No. 5,169,762 to Gray & Ullrich (hereinafter "Gray & Ullrich") and U.S. Patent No. 5,235,043 to Collins *et al.* (hereinafter "Collins"). According to the Patent Office, Gray & Ullrich teach both the amino acid and nucleotide sequence of human proNGF, methods of making NGF proteins recombinantly using either prokaryotic or eukaryotic host cells, and pharmaceutical compositions thereof. The Patent Office concedes, however, that Gray & Ullrich are silent regarding the activity of proNGF as it relates to β-NGF. The Patent Office asserts, however, that the activity of proNGF is directly related to its structure, and therefore, is an inherent property of proNGF.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully note that the Patent Office's attempt to argue inherency is misplaced in the context of a rejection under 35 U.S.C. § 103(a). The concept of inherency is not applicable to the question of obviousness. *In re Sporman*, 363 F.2d 444, 150 USPQ 449 (CCPA 1965). To state that a reference inherently teaches an element of a claim in fact rebuts any finding of *prima facie* obviousness. The concept of inherency is not properly applicable to the question of obviousness (*see In re Sporman*, 363 F.2d 444,150 USPQ 449 (CCPA 1965)).

Obviousness and inherency are entirely different questions; that which may be inherent

is not necessarily known and, therefore, is an indication of unobviousness (*In re Sporman*, 363 F.2d 444,449, 150 USPQ 449, 452 (CCPA 1965; *see also In re Naylor*, 360 F.2d 765,152 USPQ 106 (CCPA 1966); *In re Adams*, 356 F.2d 998,148 USPQ 742 (CCPA 1966); and *In re Shetty*, 566 F.2d 81,195 USPQ 753 (CCPA 1977)).

Reference to an unexpected property as inherent begs the question of whether an unexpected property rebuts *prima facie* obviousness. The unexpected property is part of the claimed subject matter as a whole, and, therefore, evidence of unobviousness of the claimed subject matter. In *In re Naylor*, a process for preparing a polybutadiene polymer having unexpected properties was at issue. The CCPA held that the fact that a rubbery polybutadiene having high 1,2-addition might be inherent in following the combined teachings of the prior art is immaterial, if one of ordinary skill in the art would not appreciate or recognize that inherent result. In *In re Adams*, the CCPA held that since properties of a claimed structure are always inherent, it is "transparently erroneous" to state that subject matter cannot be patented on the basis of an inherent property. Finally, in *In re Shetty*, the court held that "inherency is quite immaterial if, as record established here, one of ordinary skill in the art would not appreciate or recognize that inherent result."

The non-obviousness of the instantly claimed subject matter follows the reasoning of the above referenced cases. The Edwards reference explicitly teaches that human proNGF has "little or no activity". Thus, it is clear that Edwards teaches against making a pharmaceutical preparation of purified human proNGF as the active ingredient, wherein the purified human proNGF is purified to at least 90% purity and has an activity in vivo analogous to β-NGF and promotes survival of dorsal root ganglia (DRG) sensory neurons (claim 8) and/or has a biological activity in a dorsal root ganglion (DRG) assay that is about half that of human β-NGF in the same assay on a molar basis (claim 26) as set forth in the instant claims. The Patent Office has presented no evidence or other rationale to rebut the express teaching of this reference, and thus has not presented a *prima facie* case of obviousness of the instant claims.

Furthermore, the Patent Office's suppositions with respect to pro-NGF produced by eukaryotic cells also fail to support the instant rejection. Edwards sets forth in Example 6,

> Pro-NGF-beta purified from mouse L929 cells infected with VV:NGF-A and VV:NGF-B was digested with trypsin (100 ng trypsin/50 ug pro-NGF-beta) in 100 mM Tris, pH 7.6, at 37°C for 30 min. The trypsin was then inactivated, and the solution applied to dissociated chick dorsal root ganglia cells. After 18-24 hours, the presence of cell processes larger than the cell bodies was determined. Appropriate positive and negative controls were also included, using L929 supernatant from cells infected with VV:wt, supernatants from L929 infected with VV:NGF-A or VV:NGF-B but not digested, and purified mouse (non-recombinant) NGF-beta. Antisera to NGF fully blocked the activity seen from this preparation.

> The results indicate that supernatant from L929/VV:wt exhibited no NGF activity, supernatant from L929/VV:NGF-A and L929/W:NGF-B (not digested) exhibited little to no activity, and supernatant from L929/VV:NGF-A and L929/W:NGF-B digested with trypsin exhibited substantial NGF-beta activity. (Emphasis added).

Applicants respectfully submit that mouse L929 cells are eukaryotic cells, and VV:NGF-A and VV:NGF-B are vaccinia virus vectors encoding two different forms of murine pro-NGF (*see* Edwards at col. 7, lines 34-39). Since VV:NGF-A and VV:NGF-B showed "little or no activity" as explicitly stated in col. 9, lines 6-11 of Edwards, it is clear that the fact that pro-NGF has "an activity in vivo analogous to β-NGF and promotes survival of dorsal root ganglia (DRG) sensory neurons" as claimed in claim 8 or "substantial activity (*e.g.*, a biological activity in a dorsal root ganglion (DRG) assay that is about half that of human β-NGF in the same assay on a molar basis" as claimed in claim 26 is not taught.

Further, applicants respectfully submit that since the instant claims relate to pharmaceutical preparations comprising human proNGF as the active ingredient, the Patent Office's concession that Gray & Ullrich are silent regarding the activity of proNGF as it relates to β-NGF in view of the fact that recombinant and *in vitro* transcribed proNGF preparations do not inherently possess activity is clear evidence that Gray & Ullrich's disclosure of the amino acid and nucleotide sequences of human proNGF is insufficient to support the instant rejection because it provides one of ordinary skill in the art with no reasonable expectation that a human proNGF preparation *per se* would have any activity. As such, applicants respectfully submit that there is no suggestion in Gray & Ullrich to produce a pharmaceutical preparation with human proNGF as the active ingredient.

Applicants further respectfully submit that Collins does not cure this deficiency. According to the Patent Office, Collins teaches "production of purified forms of all members of the NGF/BDNF family of neurotrophic proteins which would be valuable as pharmaceutical preparations" as well as biologically active recombinant human NGF family member proteins. Here as well, however, the Patent Office concedes that Collins is silent regarding the activity of proNGF as it relates to β-NGF, again asserting that the activity of proNGF is directly related to its structure, and therefore, is an inherent property of proNGF. Given the fact that the prior art of record has established that recombinant and *in vitro* translated forms of proNGF do not necessarily have biological activity, the Collins reference, like Gray & Ullrich, does not satisfy the requirements of inherent disclosure.

Summarily, applicants respectfully submit that the Patent Office has not presented any evidence whatsoever that would provide one of ordinary skill in the art a reasonable expectation

that pro-NGF would have biological activity. Thus, the Patent Office has not presented a *prima facie* case of obviousness of Gray & Ullrich or Collins, since neither of these references provides any suggestion sufficient to overcome the explicit teachings of Edwards. In fact, applicants respectfully submit that the only data that does provide any indication that pro-NGF has such a biological activity is applicants' own disclosure, which cannot be used to provide the suggestion to combine references in support of a rejection under 35 U.S.C. § 103(a).

Accordingly, applicants respectfully submit that claims 8, 20, and 26-29 have been distinguished over Gray & Ullrich and Collins, and are thus in condition for allowance. Applicants respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

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